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GB 0750373 A EP 0271306 A2
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(54) Veterinary compositions for treating mastitis

(57) Compositions for treating mastitis in dry cows comprise an insoluble antibiotic in aqueous suspension. Administration is by the intramammary route. Antibiotic is typically cloxacillin benzathine. Compositions may further comprise a gel seal containing a heavy metal salt e.g. bismuth subnitrate.

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Bioavailability of Cloxacillin in Milk: Data for Individual Quarters(n=30) in Eight Cows following infusion of injector 1A(Aqueous Formulation)

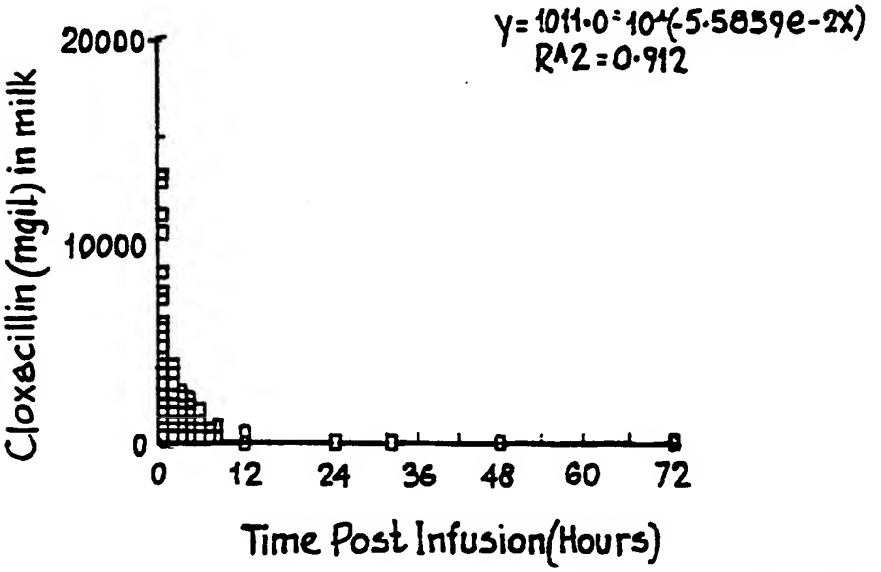
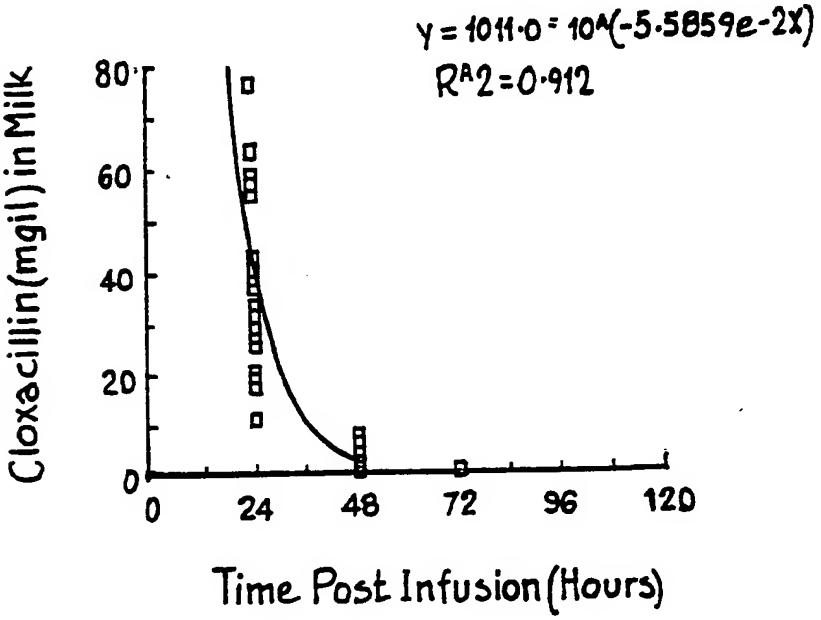


Fig. 1.1

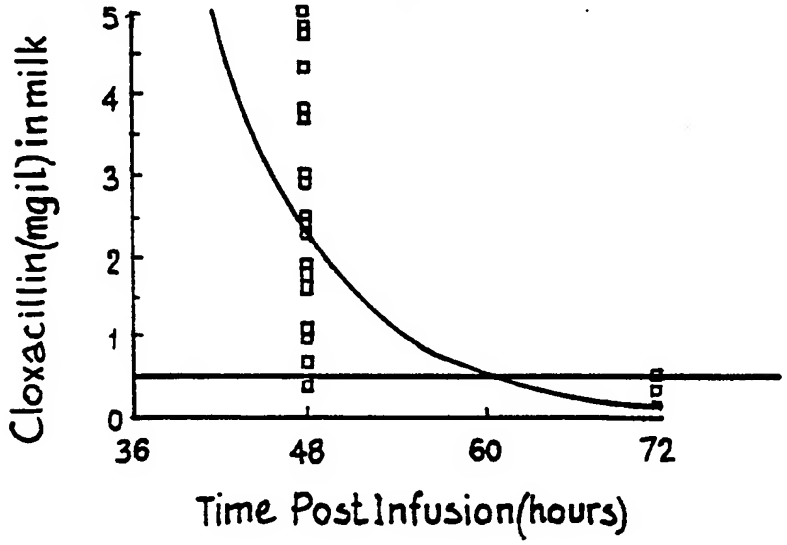
Bioavailability of Cloxacillin in Milk: Data for individual Quarters (n=30) in Eight Cows following infusion of injector 1A (Aqueous Formulation)



917824-72h Graph

Fig. 1.2

Bioavailability of Cloxacillin in Milk : Data for individual Quarters (n=30) in Eight Cows following infusion of injector 1A (Aqueous Formulation) – Terminal Elimination Phase



9178 Term Elm. Graph

Fig. 1.3

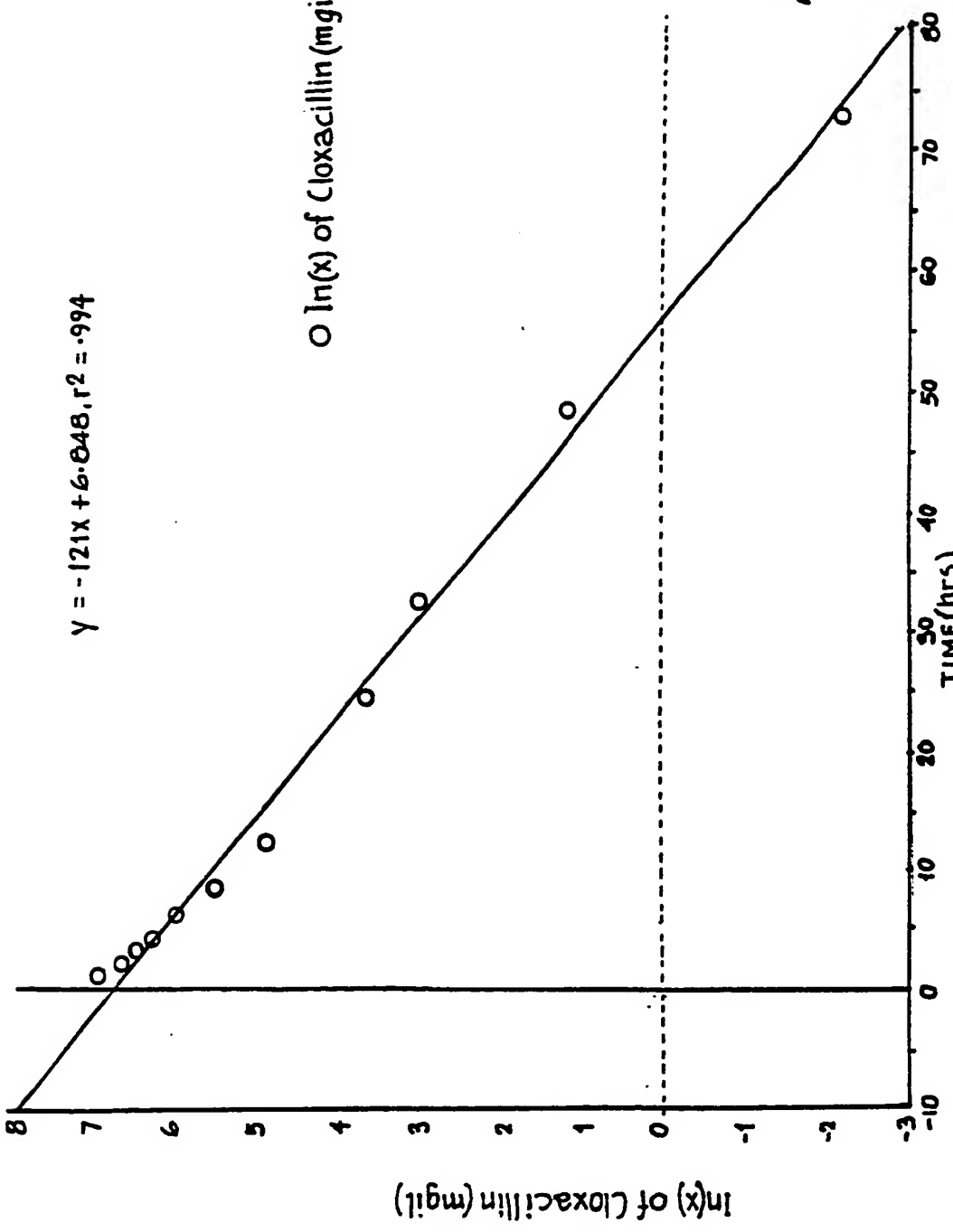

ln(x) of Cloxacillin (mgil)
8
7
6
5
4
3
2
1
0
-1
-2
-3
-10
0
10
20
30
40
50
60
70
80
TIME(hrs.)
O ln(x) of Cloxacillin (mgil)
y = -121x + 6.848, r2 = .994

Fig. 2

2273655

"A Veterinary Composition"

The invention relates to a veterinary composition, particularly for the prophylaxis and treatment of mastitis in cows.

Bacterial infection via the teats of a cow is the most common cause of mastitis.

In one aspect the invention relates to a veterinary composition for treating mastitis in dry cows.

It is known to treat teats of a cow with a long acting antibiotic with effective cover only being provided whilst minimum inhibitory concentration (MIC) levels of the antibiotic are maintained. This period of cover can vary from 4 to 10 weeks.

It is also known to provide a physical barrier in the teat canal to try to prevent the ingress of pathogens. One such system is described in UK 1,441,747 (Lazonby).

One commercially available barrier system comprises a twin injector pack, one injector containing an antibiotic formulation and a second injector containing a barrier or seal formulation. The antibiotic formulation comprises penicillin salts and dihydrostreptomycin which is infused into the udder following the last lactation and before the cow is dried off. The seal formulation comprises a gel of aluminium stearate and liquid paraffin containing approximately 35% by weight of bismuth subnitrate. This is infused into the udder after the antibiotic formulation to seal the teat canal.

In another aspect the invention relates to a veterinary composition for treating mastitis in lactating cows.

It is known to treat mastitis in lactating cows with antibiotics suspended in non aqueous bases. The antibiotics are generally administered at either 12 or 24 hour intervals over a period of days. This is not only inconvenient for the farmer or veterinary surgeon but is also stressful to the animal and increases the risk of further infection. There is a further problem in that any milk delivered from an affected cow must be withheld from human consumption for a period of up to 144 hours from the commencement of treatment.

This invention is therefore directed towards providing an improved veterinary composition for the prophylaxis and treatment of mastitis in dry cows and lactating cows.

According to the invention there is provided a veterinary composition, for intramammary use in non-human animals comprising an antibiotic in the form of a substantially insoluble salt in an aqueous suspension.

Preferably the antibiotic is an insoluble salt of a substantially synthetic penicillin, preferably cloxacillin. Most preferably the antibiotic comprises cloxacillin benzathine.

Preferably the antibiotic is in a micronised form having an average dimension of less than 25 μ. Preferably a substantial proportion of the antibiotic has an average dimension of less than 10 μ.

Preferably the composition is a unit dose. Typically the composition contains 600 mg of cloxacillin as cloxacillin benzathine.

In one embodiment of the invention the composition includes a suspension aid, such as polyvinylprollidone. In another embodiment of the invention the composition includes a buffer, such as sodium citrate.

In a preferred arrangement the composition includes a surfactant.

Most preferably the composition is in the form of an injector for intramammary administration.

The composition is especially for use in the prophylaxis or treatment of mammary disorders in lactating animals.

The invention also provides a veterinary product for intramammary use in non-human animals during an animals' dry period, the product comprising a veterinary composition according to the invention and a gel base seal formulation.

Preferably, a heavy metal salt is present in the gel base. Typically, the heavy metal salt is present in an amount of at least 40% by weight of the base, preferably between 50% and 75% by weight, most preferably approximately 65% by weight.

In one embodiment of the invention the heavy metal salt is bismuth sub-nitrate.

In one embodiment of the invention the base is a gel based on aluminium stearate. In this case preferably the gel includes a vehicle such as liquid paraffin.

In another embodiment of the invention the gel comprises a polyethylene gel. The gel may be based on low density polyethylene or on high density polyethylene.

Detailed Description of the Invention

The invention will be more clearly understood from the following description thereof given by way of example only.

EXAMPLE A - LC

A single dose veterinary composition comprising an antibiotic-containing injector for treating mastitis in lactating cows was prepared as follows :

INJECTOR 1A

Component	g/Kg	Function
*Cloxacillin Benzathine	212.6	Antibiotic
PVP	0.59	Suspension Aid
Sodium Citrate	7.87	Buffer
Tween 80	0.983	Surfactant
EDTA (disodium)	0.0787	Cation Scavenger
Antifoam M30	0.0157	Production Aid
Water for Injection	QS	Aqueous Vehicle

* (i) will be adjusted depending on potency.

(ii) the cloxacillin benzathine was in a micronised form having an average dimension less than 25μ

with approximately 75% less than 15μ and 50% less than 10μ and 85% was greater than 2μ.

(1) Place most of the water for injection in a production vessel.

(2) Add and dissolve separately, sodium citrate, E.D.T.A., P.V.P. and Tween 80. Mix well.

(3) Add antifoam and mix well, the solution will have a slight haze.

(4) Add and suspend Cloxacillin Benzathine and homogenise for 15 minutes.

(5) Bring to final weight with addition of further water for injection.

(6) Fill 3.6g into intramammary injectors.

All of the above steps are carried out under normal aseptic conditions.

This formulation is stable when subjected to extended storage periods in its proposed marketing container.

We have surprisingly found that once infused by the intramammary route cloxacillin benzathine in an aqueous base gives rapid absorption in a very short time period.

A number of studies have been conducted in cows to establish the following : -

Study 1: Bioavailability of cloxacillin in bovine colostrum following intramammary infusion of Injector 1A.

Study 2: Irritancy of aqueous cloxacillin in the bovine mammary gland.

The results can be summarised as follows.

INJECTOR 1A - Study 1

The primary objective of this study was to demonstrate the bioavailability of cloxacillin in the bovine udder after the infusion of an aqueous formulation of Cloxacillin Benzathine. As a secondary objective plasma levels of Cloxacillin were also measured, in order to assess the extent of systemic absorption.

Eight animals were infused with Injector 1A in all four quarters, and samples of milk were taken at the following intervals post infusion : 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 32, 48, 72, 96, 120 and 144 hours.

Quarter results were recorded for all animals (it was not possible to get samples from two of the quarters due to problems associated with hand milking of animals normally used to being machine milked). Not surprisingly there was a large variation in the amount of drug found, even between quarters of the same animal. A peak mean value of 5233.4 mg/L was found at the first sampling interval (0.5 hr) with an approximately exponential decline being noted over the next 72 hours. The results indicate that the antibiotic was extensively distributed throughout the mammary gland, as significant amounts of drug were still found at 24, 32 and 48 hours post the initial infusion, despite the removal of drug at each milking.

In addition, the level of a systemic absorption of Cloxacillin was assessed by monitoring levels of drug in the plasma. Sampling intervals were identical to those

for the milk study except that a further four samples were taken at 168, 192, 216 and 240 hours post infusion.

The amount of drug detected in the plasma of treated animals peaked at between 6-8 hours at a mean of 0.15 mg/L. The highest level seen in any animal was 0.22 mg/L. By 96 hours post infusion drug was detectable in one animal only, and it continued to be detectable in that animal for a further 144 hours. This animal also had drug present in its pre-dose plasma sample and would seem to be somewhat of an outlier. However, as no drug was detected in its pre-dose milk sample nor was it any different in its elimination of drug from the milk, it was considered valid to include it in the set of results.

This study indicates that a Cloxacillin Benzathine aqueous formulation has the desired characteristics of producing rapid absorption and distribution within the udder, producing large peak concentrations of drug followed by a swift removal of the antibiotic from the bovine mammary gland, as evidenced by the fact that no drug was detectable in the quarter of any animal 144 hours post infusion.

Figure 1.1, 1.2 and 1.3 are graphic representations of the results of this study.

Fig 2: is a log transformation of the results of Figure 1.1.

<u>Study 2.</u>

Injector 1A was mildly irritant to the bovine udder when used as an intramammary infusion. However, any rise in somatic cell counts were transitory in nature and all animals had returned to normal within 72 hours of the

infusion of the product. Hence it can concluded that this formulation is suitable for use as a lactating intramammary.

By providing an insoluble salt of a synthetic penicillin such as cloxacillin benzathine in a micronised form in an aqueous base we have achieved in a single dose a high initial peak of antibiotic within 30 minutes of administration which is maintained at therapeutic levels for up to 72 hours. Within 30 minutes the antibiotic administered also crosses the blood-milk barrier establishing a drug reservoir which aids the maintenance of therapeutic levels of cloxacillin for the 72 hour treatment period. This is particularly important where there is a systemic involvement in the mastitic condition. All the above is achieved with a single dose.

EXAMPLE A -DC

A veterinary composition for treating mastitis in dry cows was prepared. The twin-pack composition comprised an antibiotic-containing injector and a seal-containing injector. The antibiotic-containing injector was the same as the injector 1A described above. The injector 1A is suitable for dry cow therapy in association with a teat seal, providing as it does high initial peaks of cloxacillin followed by a rapid elimination phase of the drug. Studies 1 and 2 above confirm this. The following additional study was also carried out specifically for dry cow applications to assess the residues of cloxacillin in bovine colostrum following intramammary infusion of the antibiotic injector. The second seal-containing injector (2A) is described below.

INJECTOR 1A - Study 3

Study 3 was conducted to specifically determine the end point for milk withholding. Animals were infused in each of four quarters with the Injector 1A. Samples were taken every 24 hours and analysed for cloxacillin levels. Eight days after administration of Injector 1A the levels of drug were below the acceptable maximum residue level for cloxacillin.

INJECTOR TYPE 2A

Various gels based on liquid paraffin with aluminium stearate were prepared.

Formulation	Mass Constituents	YV/(Nm^{-2})
2A1	3.5g 14% AS-LP gel + 37%BSN + 0.1%Ac	110.3
2A2	7.0g 14% AS-LP gel + 37%BSN + 0.1%Ac	110.3
2A3	3.5g 14% AS-LP gel + 37%BSN + 0.1%Ac	215.5

LP = Liquid Paraffin
BSN = Bismuth Subnitrate
Ac = Acriflavin
AS = Aluminium Monostearate
YV = Yield value - (A measure of the relative fluidity of the gel. Low yield values indicate a more liquid gel).

Products 2A1 to 2A3 were considered appropriate candidates for use as test seals.

An ideal teat seal should have the following characteristics :

1. It should be non-irritant to the bovine udder;

2. Persistence - the seal should remain in situ for the duration of the dry cow period;

3. Consistency - the seal should not break up within the udder;

4. Compatibility - the seal should be compatible with the antibiotic formulation used in association with it, either aqueous or oily;

5. Ease of Removal - at the end of the dry period, the seal should be readily removable for the udder and not give rise to persistent residues of either the seal or antibiotic.

Irritancy of the seals was the first characteristic to be assessed as any product which was irritant would have to be rejected irrespective of its performance against the other criteria. Irritancy was measured by conducting somatic cell counts in treated and untreated quarters of lactating cows and comparing these results by measuring area under the curve ratios using the following formula:

$$\text{AUC Ratio} = \frac{\text{AUC of treated quarter}}{\text{AUC of untreated quarter}}$$

This allows for a relative assessment of the various seal formulae.

Formulation	AUC Ratio	Peak (cells/ml)	Condition of milk	Duration before return to pre-dose level (hours)
2A1	1.25	9.0×10^5	Normal	160
2A2	1.33	1.0×10^6	Normal	144
2A3	1.28	8.5×10^5	Normal	160

Formulations 2A1 and 2A3 were considered appropriate for further investigation. It was concluded that AS-LP gels are viable candidates for sealing teats.

In vitro studies have shown that whilst AS-LP gels have relatively high yield values, their tensile strength is not as great as other possible seal formulations. The relative merits of these two properties were studied by X-ray analysis of various formulations in dry cows.

A series of studies were undertaken to optimise these parameters :

INJECTOR TYPE 2A - Study 1

Formulation	Gel former %	LP %	AC %	BSN %	Mass(g)	P g cm^3	YV Nm^{-2}
2A1	8.8 AS	54.1	0.1	37	7.0	1.32	110.0

AS = Aluminium Stearate
LP = Liquid Paraffin
AC = Acriflavin
BSN = Bismuth Subnitrate
p = Density
YV = Yield Value

The test formulation was infused into quarters of dry cows. The effectiveness of sealing was measured by X-ray analysis. In addition the mass of seal recovered, % BSN recovered and the effective seal duration [ESD] were estimated.

Formulation	ESD (days)	Mass of seal recovered (%)	BSN recovered
2A	28.5 ± 13.1	8.19 (117.1)	64.1

The mass of seal recovered was in excess of that applied probably due to the presence of aqueous material.

INJECTOR TYPE 2A - Study 2

The effect of the product volume and density was examined in another series of X-ray studies.

Formulation	Gel former %	LP %	AC %	BSN %	Mass g	P g cm^3	YV Nm^{-2}
2A4	3.1 AS	31.8	0.1	65	5.0	1.70	161.7
2A5	3.1 AS	31.8	0.1	65	10.0	1.70	161.7

The results of these studies are shown in the table below:

Formulation	Mass(g)* recovered (%)	% BSN ** recovered
2A4	2.47 (49.4)	89.8
2A5	4.52 (45.2)	100.2

* Adjusted for water content

** % BSN were higher than in the previous study indicating a greater integrity of seal. As this trial was of a shorter duration than study 1, this may have been a contributing factor. However, increasing the density and reducing the volume had a clearly beneficial effect on the product performance.

INJECTOR TYPE 2A - Study 3

As it is intended to use the teat seal in conjunction with an antibiotic preparation this study looked at the effect of an aqueous and oily based antibiotic suspension on seal integrity over time. Additionally, the mass of seal was reduced to 3.5g to see if this could further enhance the seals effectiveness.

Products used are given in the table below :

Formulation	Gel former %	LP %	Ac. %	BSN %	Mass g	P g/cm^3	YV NM^{-2}	Anti-biotic
2A6	3.1% AS	31.8	0.1	65	3.5	1.70	161.7	Oily
2A6^1	3.1% AS	31.8	0.1	65	3.5	1.70	161.7	Aq.

The products were then examined for their effective seal duration [ESD].

Formulation	ESD (days)	Recovery of material (g)	BSN Recovery %	BSN recovery in fluid portion ppm
2A6	47.8 ± 13.5	0	0	2191
2A6^1	63.3 ± 5.4	2.06	75.2	117

A combination of a seal and an aqueous based antibiotic offers a superior combination to a seal and an oily based antibiotic. This can be deduced from the fact that the ESD's for the seal/aqueous combinations were significantly better than those for oily combination. This is further evidenced by the high BSN recoveries (>75%) for the aqueous products, indicating retention of seal in situ. In contrast, the amount of bismuth found in the fluid portion at parturition was far lower for the aqueous than the oily combination. This shows that there was a larger

degree of dispersal of the seal into the udder with the oily combinations.

The amount of BSN lost in absolute terms can be calculated as follows :

A x B x M	=	Loss of BSN (g)
A	=	% BSN lost.
B	=	% of BSN in product
M	=	Mass of Product

Using the formula, product 2A1 lost 1.30 g. 2A6[1] lost 0.57g. Considering that product 2A6[1] was in situ for 70 days as compared to 49 days for 2A1, this demonstrates at least a 2-3 fold reduction in BSN loss and a major improvement in product design.

PREFERRED METHOD OF MANUFACTURE FOR INJECTOR TYPE 2A

	Gm/Kg
Aluminium Stearate (Alugel 30 D.F.)	48.9
Heavy Liquid Paraffin	300.4
Bismuth Subnitrate	650.00
Acriflavin (Pigment)	0.994

Each injector contains 3.5g.

The aluminium stearate used is a distearate compound having a melting point in the region of 150°C to 160°C.

Bismuth subnitrate ($6Bi_2O_3.5N_2O_5.9H_2O$) is a white, slightly hydroscopic powder.

(1) Place heavy liquid paraffin in reactor vessel. heat to 160°C for one hour. Cool to 40°C.

(2) Start emulsifiers and mixers and add the aluminium stearate. Heat to 145°C ± 5°C and maintain for one hour. Cool to 40°C.

(3) Add and blend the Bismuth Subnitrate and Acriflavin.

(4) Fill 3.5 g into intramammary injector.

EXAMPLE B

A veterinary composition was prepared comprising a first antibiotic-containing injector having the same formulation as Injector 1A described above and a second seal injector 2B as described below.

INJECTOR TYPE 2B

Various gel based on liquid paraffin with polyethylene were prepared. Two grades of polyethylene were used in manufacturing the gels: low density (LDPE) and high density (HDPE). They differed in the degree of side chain branching but produced similar gels.

Formulation	Mass	Constituents	YV (NM^{-2})
2B1	3.5g	3% HDPE - LP gel + 37% BSN + 0.1%Ac	40.9
2B2	7.0g	3% HDPE - LP gel + 35% BSN + 0.1%Ac	40.9
2B3	7.0g	5% HDPE - LP gel + 37% BSN + 0.1%Ac	110.0
2B4	7.0g	5% HDPE - LP gel + 37% BSN + 0.1%Ac	220.3
2B5	3.5g	3% HDPE - LP gel + 37% BSN + 0.1%Ac	65.8
2B6	7.0g	3% HDPE - LP gel + 37% BSN* + 0.1%Ac	36.6
2B7	7.0g	3% LDPE - LP gel + 37% BSN* + 0.1%Ac	54.1

LP = Liquid Paraffin

BSN= Bismuth Subnitrate

Ac = Acriflavin

YV = Yield value - (A measure of the relative fluidity of the gel. Low yield values indicate a more liquid gel).

* = BSN was in micronised form.

Products 2B1 and 2B7 were considered appropriate candidates for use as test seals. An ideal teat seal should have the following characteristics:

1. It should be non-irritant to the bovine udder;

2. Persistence - the seal should remain in situ for the duration of the dry cow period;

3. Consistency - the seal should not break up within the udder;

4. Compatibility - the seal should be compatible with the antibiotic formulation used in association with it, either aqueous or oily;

5. Ease of Removal - at the end of the dry period, the seal should be easily removable for the udder and not give rise to persistent residues of either the seal or antibiotic.

Irritancy of the seals was the first characteristic to be assessed as any product which was irritant would have to be rejected irrespective of its performance against the other criteria. Irritancy was measured by conducting somatic cell counts in treated and untreated quarters of lactating cows and comparing these results by measuring area under the curve ratios using the following formula:

AUC Ratio = $\frac{\text{AUC of treated quarter}}{\text{AUC of untreated quarter}}$

This allows for a relative assessment of the various seal formulae.

Formulation	AUC RATIO	PEAK (CELLS/mL)	CONDITION OF MILK	DURATION BEFORE RETURN TO PRE-DOSE LEVEL (HOURS)
2B1	17.0	5.3×10^6	N	160
2B2	4.8	2.4×10^6	N	160
2B3	16.4	$>3 \times 10^5$	N	184
2B4	3.7	1.7×10^6	N	136
2B5	10.8	1.0×10^6	N	112
2B6	13.0	7.0×10^6	N	120
2B7	51.8	$>1.0 \times 10^7$	C	112

N = Normal

C = Clotted

Formulations 2B1 and 2B5 were considered appropriate for further investigation. 2B6 and 2B7 (micronised Bismuth Subnitrate) were excluded on the basis of there being more irritant that the other formulas tested and having no significant advantages. Thus, it is concluded that PE-LP gels are viable candidates for sealing teats.

In vitro studies have shown that PE-LP gels have high tensile strengths for relatively low yield values. The merits of these two properties were studies by X-ray analysis of various PE-LP formulations in dry cows.

A series of studies were undertaken to optimise these parameters:

INJECTOR TYPE 2B - Study 1

Formulation	Gel former %	LP %	Ac. %	BSN %	Mass g	P g/cm^3	YV NM^{-2}
2B3	3.1% PE	59.8	0.1	37	7.0	1.32	136.6
2B2	1.9% PE	61.0	0.1	37	7.0	1.32	40.0
2B3[1]	3.1% PE	59.8	0.1	37	7.0	1.32	220.3

PE = Polyethylene
LP = Liquid Paraffin
AC = Acriflavin
BSN= Bismuth Subnitrate
P = Density
YV = Yield Value
2B3[1]= Formulation is identical to 2B3. Gel was formed using different temperature profile, leading to different yield values.

Each of the test formulations was infused into quarters of dry cows. The effectiveness of sealing was measured by X-ray analysis. In addition to mass of seal recovered, % BSN recovered and the effective seal duration [ESD] were estimated.

Formulation	ESD (days)	Mass of Seal recovered (%)	BSN recovered
2B3	47.3 ± 16.0	0.62 (8.81)	40.8
2B2	54.1 ± 10.4	3.00 (43.0)	40.0
2B3[1]	49.0 ± 12.9	1.38 (19.7)	44.6

There was a direct correlation between the ESD and the mass of seal recovered for these products.

INJECTOR TYPE 2B- Study 2

The effect of the product volume and density was examined in another series of X-ray studies.

Formulation	Gel former %	LP %	Ac. %	BSN %	Mass g	P g/cm^3	YV NM^{-2}
2B8	1.7% PE	33.2	0.1	65	5.0	1.70	216.3
2B9	1.7% PE	33.2	0.1	65	10.0	1.70	216.3

The results of these studies are shown in table below:

Formulation	Mass (g) * recovered (%)	% BSN ** recovered
2B8	3.78 (75.6)	85.6
2B9	3.92 (39.2)	92.2

* Adjusted for water content

** % BSN were greater than in the previous study indicating a greater integrity of seal. As this trial was of a shorter duration than study 1, this may have been a contributing factor. However, increasing the density and reducing the volume had a clearly beneficial effect on the product performance.

INJECTOR TYPE 2B - Study 3

As it is intended to use the teat seal in conjunction with an antibiotic preparation this study looked at the effect of an aqueous and oily based antibiotic suspension on seal integrity over time. Additionally, the mass of seal was reduced to 3.5g to see if this could further enhance the seals effectiveness.

Products used are given in the table below:

Formulation	Gel former %	LP %	Ac. %	BSN %	Mass g	P g/cm^3	YV NM^{-2}	Anti-biotic
2B8	1.7% PE	33.2	0.1	65	3.5	1.70	216.3	Oily
2B9	1.7% PE	33.2	0.1	65	3.5	1.70	216.3	Aq.

The products were then examined for their effective seal duration [ESD].

Formulation	ESD (days)	Recovery of material (g)	BSN Recovery %	BSN Recovery in fluid proportion ppm
B8	56.8 = 13.9	0	0	1200
B9	60.3 = 8.2	0.793	77.6	147

A combination of seal and a non aqueous based antibiotic offers a superior combination to seal and an oily based antibiotic. This can be deduced from the fact that the ESD's for the seal/aqueous combinations were significantly better than those for oily combinations. This is further evidenced by the high BSN recoveries (>75%) for the aqueous products, indicating retention of seal in situ. In contrast the amount of bismuth found in the fluid portion at parturition was far lower for the aqueous than the oily combination. This shows that there was a larger degree of dispersal of the seal into the udder with the oily combinations.

In conclusion, the use of polyethylene as a gelling agent in combination with heavy metal salts in a teat seal product in combination with an aqueous based antibiotic system provides a product with the desired properties as earlier outlined which should be efficacious in the treatment and prophylaxis of dry cow mastitis.

PREFERRED METHOD OF MANUFACTURE FOR INJECTOR TYPE 2B

	Gm/Kg
H.D.P.E.	17.00
Heavy Liquid Paraffin	332.00
Bismuth Subnitrate	650.00
Acriflavin (Pigment)	0.994

Each injector contains 3.5g.

(1) Place heavy liquid paraffin in reactor vessel. Heat to 160°C for one hour. Cool to 40°C.

(2) Start emulsifiers and mixers and add the H.D.P.E. Heat to 145°C ± 5°C and maintain for one hour. Cool to 40°C.

(3) Add and blend the Bismuth Subnitrate and Acriflavin.

(4) Fill 3.5g into intramammary injector.

In vitro work has shown that polyethylene based gels have tensile strengths and yield values that may make them suitable candidates as sealing agents with low levels or possibly zero levels of heavy metal salts. One such injector type 2C may be prepared as follows:

INJECTOR TYPE 2C

	g/Kg
Polyethylene	30.000
Liquid Paraffin	969.000
Acriflavin	1.000

1) Mix Polyethylene Beads and Liquid Paraffin for 20 minutes.

2) Heat mixture 140°C ± 5°C for one hour with continuous stirring.

3) Allow to cool to room temperature whilst stirring.

4) Add and blend to Acriflavin.

5) Fill 3.5g into intramammary injectors.

The invention is not limited to the embodiments hereinbefore described which may be varied in detail.

CLAIMS

1. A veterinary composition for intramammary use in non-human animals comprising an antibiotic in the form of a substantially insoluble salt in an aqueous suspension.

2. A veterinary composition as claimed in claim 1 wherein the antibiotic comprises a substantially insoluble salt of a synthetic penicillin.

3. A veterinary composition as claimed in claim 2 wherein the synthetic penicillin is cloxacillin.

4. A veterinary composition as claimed in claim 1, 2 or 3 wherein the antibiotic comprises cloxacillin benzathine.

5. A veterinary composition as claimed in any preceding claim wherein the antibiotic is in a micronised form having an average dimension of less than 25 μ.

6. A veterinary composition as claimed in claim 4 wherein a substantial proportion of the antibiotic has an average dimension of less than 10 μ.

7. A veterinary composition as claimed in any preceding claim wherein the composition is a unit dose.

8. A veterinary composition as claimed in claim 5 wherein the composition contains 600 mg of cloxacillin as cloxacillin benzathine.

9. A veterinary composition as claimed in any preceding claim wherein the composition includes a suspension aid.

10. A composition as claimed in claim 9 wherein the suspension aid is polyvinylpyrollidone.

11. A composition as claimed in any preceding claim wherein the composition includes a buffer.

12. A composition as claimed in claim 11 wherein the buffer is sodium citrate.

13. A composition as claimed in any preceding claim wherein the composition includes a surfactant.

14. A veterinary composition as claimed in any preceding claim in the form of an injector for intramammary administration.

15. A veterinary composition as claimed in any preceding claim for use in the prophylaxis or treatment of mammary disorders in lactating animals.

16. A veterinary composition substantially as hereinbefore described with reference to Example A-LC and the drawings.

17. A veterinary product for intramammary use in non-human animals during an animals' dry period, the product comprising a veterinary composition as claimed in any of claims 1 to 14 or 16 and a gel base seal formulation.

18. A veterinary composition as claimed in claim 17 wherein a heavy metal salt is present in the gel base.

19. A veterinary composition as claimed in claim 18 wherein the heavy metal salt is present in an amount of at least 40% by weight of the base.

20. A veterinary composition as claimed in claims 18 or 19 wherein the heavy metal salt is present in an amount of between 50% and 75% by weight of the base.

21. A veterinary composition as claimed in any of claims 18 to 20 wherein the heavy metal salt is present in an amount of approximately 65% of weight of the base.

22. A veterinary composition as claimed in any of claims 18 to 21 wherein the salt is bismuth sub-nitrate.

23. A veterinary composition as claimed in any of claims 17 to 22 wherein the base is a gel based on aluminium stearate.

24. A veterinary composition as claimed in claim 23 wherein the gel includes a vehicle such as liquid paraffin.

25. A veterinary composition as claimed in any of claims 17 to 22 wherein the gel comprises a polyethylene gel.

26. A veterinary composition as claimed in claim 25 wherein the gel is based on low density polyethylene.

27. A veterinary composition as claimed in claim 25 wherein the gel is based on high density polyethylene.

28. A veterinary composition substantially hereinbefore described with reference to the examples and drawings.

Patents Act 1977 Examiner's report to the Comptroller under Section 17 (The Search report) -27-	Application number GB 9325184.1
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Databases (see below) (i) UK Patent Office collections of GB, EP, WO and US patent specifications. (ii) ONLINE DATABASES: WPI, CLAIMS, CAS ONLINE, JAPIO, BIOSIS, EMBASE, MEDLINE	Documents considered relevant following a search in respect of Claims :- 1-38

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E: Patent document published on or after, but with priority date earlier than, the filing date of the present application.

&: Member of the same patent family; corresponding document.

Category	Identity of document and relevant passages		Relevant to claim(s)
Y	GB 1456349	(UPJOHN) see Claims 1 and 7 page 2 lines 15-32	17
X	GB 1455296	(BEECHAM) see Claims 1, 7, 13 Page 2 lines 110 etc	1-8,15
Y	GB 1441747	(LAZONBY) see whole document	18,22
X	GB 1312918	(BEECHAM) see Claims 1, 8 and page 2 lines 47-52	1,2,4,15
X	GB 0864100	(PFIZER) see Claims 1, 3 page 2 lines 75-93	1,2,9-12
X	GB 0773637	(BRISTOL) see Claims 15-25, page 1 lines 17-19, page 4 lines 42 etc	1,2,9-13
X	BRITISH VETERINARY CODEX (1965) page 571 see under benzathine penicillin		1,2,9
X	GB 0750373	(PFIZER) see Claims. Examples, page 3 lines 21 etc	1,2,9, 11-13
Y	EP 0271 306 A2	(BEECHAM) see Claims page 2 lines 51-53	23,24

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